Bulletin Penelitian Kesehatan
Health Studies in Indonesia

Vol. IV No. 1 & 2
1976.

RESPONSE OF FALCIPARUM MALARIA TO A STANDARD REGIMEN OF CHLOROQUINE IN JAYAPURA, IRIAN JAYA

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Untuk pertama kalinya di Indonesia, resistensi chloroquine terhadap Plasmodium falciparum telah dilaporkan oleh J. Verdrager dan Arwati pada tahun 1974. Distribusi yang pasti tentang adanya resistensi chloroquine terhadap P. falciparum di Asia Tenggara, khususnya di Indonesia, belumlah begitu jelas. Akan tetapi kelihatannya resistensi ini terdapat di daerah-daerah dimana A. balabacensis sebagai vector. Faktor-faktor lain yang mempengaruhi resistensi ini ialah intensitas transmisi dan penggunaan obat-obat anti malaria yang meluas, terutama pada penduduk yang tak mempunyai kekebalan. Keadaan seperti digambarkan diatas terutama tentang intensitas transmisi yang cukup tinggi terdapat di Irian Jaya dimana vector utama adalah A. punctulatus group.

Dari 35 penderita yang di-follow-up, diperoleh 7 orang yang resisten tingkat RI. Seorang diantaranya timbul bentuk asexual dari parasit pada hari ke-9, dan ke-enam lainnya pada hari ke-21 setelah makan obat chloroquine dengan dosis sesuai dengan standard WHO.

Resistance of *Plasmodium falciparum* to 4 aminoquinolines in Indonesia has recently been reported by Verdrager & Arwati (1974, 1975). After a normal intial response the asexual parasites were found to be resistant at the RI level to a standard regimen of 1500 mg amodiaquine base and/or to a standard regimen of 1500 mg chloroquine base. The infections were contracted respectively near Samarinda and near Balikpapan in the eastern part of Kalimantan (formerly Borneo), in forest areas where the vector is suspected to be *A. balabacensis.*

The exact geographical distribution of chloroquine resistance in South-eastern Asia is uncertain but seems to predominate in areas where *A. balabacensis* is the vector. A probable explanation is based on the vectorial capacity of this mosquito, resulting in intense *P. falciparum* transmission and the movement of persons from non-endemic areas (due to the limitation of *A. balabacensis* to the forest biotope, the most severe conditions prevail only in areas actually covered by jungles). The more intense is the transmission, the more intense will be the drug pressure applied in the human community, especially among the non-immune subjects, and the more rapidly would one expect the drug resistant strain to emerge. For example, in the main chloroquine resistant focus of the Khmer Republic (Cambodia), gem mining Pailin forest area, all these factors exist: intense transmission, constant influx of non-immune subjects from the neighbouring non-endemic areas and intense drug pressure, both from the previous pyrimethamine-chloroquine medicated salt project and from individual consumption of freely available chloroquine.

Similar conditions, intense transmission associated with widespread movements of non-immune workers and intense drug pressure, are also encountered in other parts of the world. One example being the Amazon area of Brazil where chloroquine resistance is well known. Another example is Irian Jaya (Indonesia New Guinea) where intense transmission is maintained by the *A. punctulatus* group, where "transmigration" from Java, Sulawesi and other parts of Indonesia is encouraged by

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Received 10 Nopember 1975.

the government and where, as in Cambodia and the Amazon, a pyrimethamine-chloroquine salt project was carried out near the capital Jayapura (Meuwissen, 1961). For those reasons it was decided early in 1973, in cooperation with the National Institute of Health Research, and Development to carry out chloroquine sensitivity tests in Irian Jaya.

The study was conducted in November 1974 in the outskirts of Jayapura, capital of the Province of Irian Jaya, located on the north coast of the island of New Guinea, close to the Papua border (see map, fig. I). Some control measures have been carried out in this area since 1971, including house spraying with DDT wp. 75 per cent and mass drug administration with chloroquine-pyrimenthamine at 6 monthly intervals. Results have been unsatisfactory.

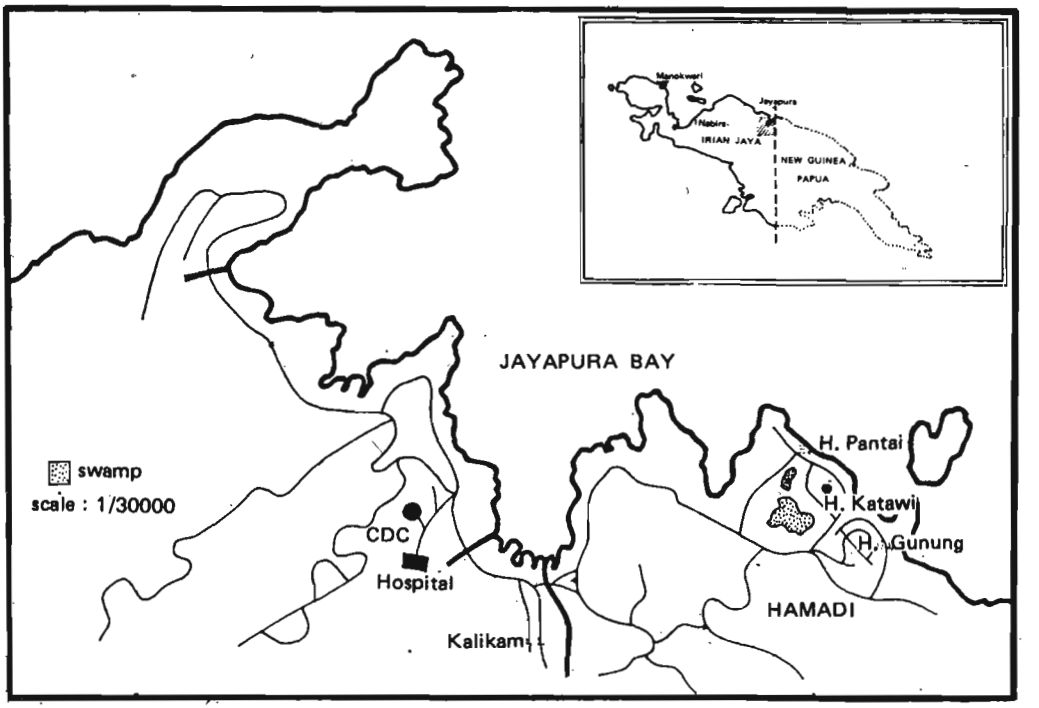

Figure I Map of Jayapura.

Earlier reports (Meuwissen, 1961) mention that "three months after the initiation of a test project wherein pyrimethaminized salt was distributed among the population in a holoendemic malaria region in Netherland New Guinea, *P. falciparum* developed resistance to pyrimethamine". There was also cross resistance to proguanil. This study was carried out in Arso approximately 30 km south of Jayapura. Chloroquine was then added to the salt.

It is to be noted that neither chloroquine nor pyrimethamine resistance has yet been reported in neighbouring Papua New Guinea (Peters, 1974).

Prior to the study and with the objective of finding suitable subjects for the test, blood surveys were carried out in different areas of Jayapura.

In Kalikamp where imigrants from Sulawesi were recently settled and were said to have experienced severe attacks of malaria.

In different areas of Hamadi, the eastern outskirt of Jayapura. Hamadi Gunung is located on a small hill, while Hamadi Pantai and Kotawi are located at sea level and close

to swampy areas where kangkung, an aquatic plant, is grown. Those are the main breeding places of *A. farauti* and *A. koliensis* in this area. In Hamadi Pantai many houses are built on stilts on the sea.

Resultas of the surveys which were used for the selection of the subjects for the test are given in table 1.

Table 1 Results of surveys in different areas of Jayapura.

Location	Slides examined	Positive (percent)	F	V	M	Mix
Kalikamp	132	12 (9)	2	8	2	–
Hamadi Gunung	270	44 (16)	16	28	–	–
Hamadi Pantai	118	62 (52)	28	27	1	6
Hamadi Kotawi	100	24 (24)	7	17	–	–

One patient from Kalikamp was admitted to hospital for study but could only be followed up until day 6. He then left the hospital and Jayapura. Therefore all our survey cases, who were treated in the field and followed up for a sufficient time, originated in Hamadi. In addition a few cases available in the provincial hospital were also tested.

MATERIALS AND METHODS

WHO standard field test procedures for assessing drug response (WHO, 1973) were followed. The object of this test being to determine the response of the local strain of *P. falciparum* to a standard dosage of chloroquine (25 mg/kg over 3 days). Chloroquine phosphate tablets (Avloclor, 150 mg base) were administered by the malariologists and swallowed with some tea or water. A minimum of 25 mg kg over 3 days, starting on day 0, was given according to table 2.

When the weight of the patient was between two of the weights indicated in the table, the dose given as the one corresponding to the highest weight. For example a patient 33 kg. was given the dosage corresponding to 37.5 kg. Moreover when fractions of tablets (halves or quarters) had to be given, only the larger part was administered, the other one being discarded.

Table 2 Dosage of chloroquine according to body weight.

Body Weight (in kg)	Dosage in mg. base (number of tablets)		
	Day 0	Day 1	Day 2
7.5	75 (1/2)	75 (0,5)	37.5 (0,25)
15	150 (1)	150 (1)	75 (0.5)
22.5	225 (1.5)	225 (1.5)	112.5 (0.75)
30	300 (2)	300 (2)	150 (1)
37.5	375 (2.5)	375 (2.5)	187.5 (1.25)
45	450 (3)	450 (3)	225 (1.5)
52.5	525 (3.5)	525 (3.5)	262.5 (1.75)
60	600 (4)	600 (4)	300 (2)

Duplicate thick and thin films were taken daily up to at least day 7 and again on day 14 and 21. Films were stained with Giemsa. The parasite count was estimated by counting the parasites against 200 or more leucocytes, depending on the density.

Excretion of chloroquine in urine was determined by Mayer-Tanret reagent (Wilson and Edeson test). Very young children and patients with very low parasitaemia were excluded.

RESULTS

Among the 60 patients originally selected for the test only 35 received the full treatment and could be followed up for at least 7 days. Among these 35 subjects 7 were found again positive during the follow-up. One experinced, twice an early recrudescence and the other 6 were found again positive on day 21. Test are summarized in table 3, and details on the patients found again positive are given in table 4.

Table 3 Tests for P. falciparum strain sensitivity to a standard dosage of chloroquine, Jayapura, Irian Jaya.

Day	0	1	2	3	4	5	6	7	14	21
No. examined	35	35	35	35	35	35	35	35	35	28
No. positive (asexual parasites)	35	25	10	4	0	0	0	0	1	7

Table 4 Cases found again positive during the test to falciparum strain sensitivity to a standard dos of chloroquine in Jayapura,

No.	Area	Sex	Age	Body Weight	Urine test on day 0	1	No of trophozoites on day 1	0	1	2	3	4	5	6	7	Period of follow up	Positive again on day	No. of trophozoites per mm³
1.	Hamadi Gunung	M	14	35	–	+	23100	3920	4325	420	0	0	0	0	0	21	21	2030
2.	Hamadi Gunung	F	15	38	–	+	55090	3815	1065	4550	70	0	0	0	0	21	21	3630
3.	Hamadi Gunung	F	40	40	+	+	560	3570	560	10	10	0	0	0	0	21	21	1365 (I)
4.	Hamadi Gunung	M	7	18	–	+	6160	3010	0	0	0	0	0	0	0	21	21	140
5.	Hamadi Gunung	F	5	13	–	+	32660	105	19505	875	0	0	0	0	0	24	11	980 (II)
6.	Hamadi Pantai	M	11	29	–	+	275	35	70	0	0	0	0	0	0	21	21	1
7.	Apo	M	21	50	–	+		17780	770	1435	35	0	0	0	0	21	21	5565 (III)

(I) Already treated in Helath Centre.
(II) Details in table 5, Fig. II & text.
(III) Hospital patient.

Patient with early recrudescence (No. 5):

This young patient, age 5, is one of the daughters of the Hamadi Gunung chief and was the first sick person to be spotted since the Hamadi Gunung survey was carried out in the house of her father. Other members of the family were healthy and had negative blood smears.

On 21 November 1974, day 0 of the first test she was seriously ill, with high fever, sweating, headache, enlarged spleen (Hacket 2) but no vomiting. An urine test could no be done but was positive the following day. She improved rapidly and on day 3 wa playing and asexual parasites had completely disappeared. Smears remained negative up to day 7. She was seen again on day 11 and found again positive with approximately 100 asexual parasites per mm³ (see details in table 5 and fig. II).

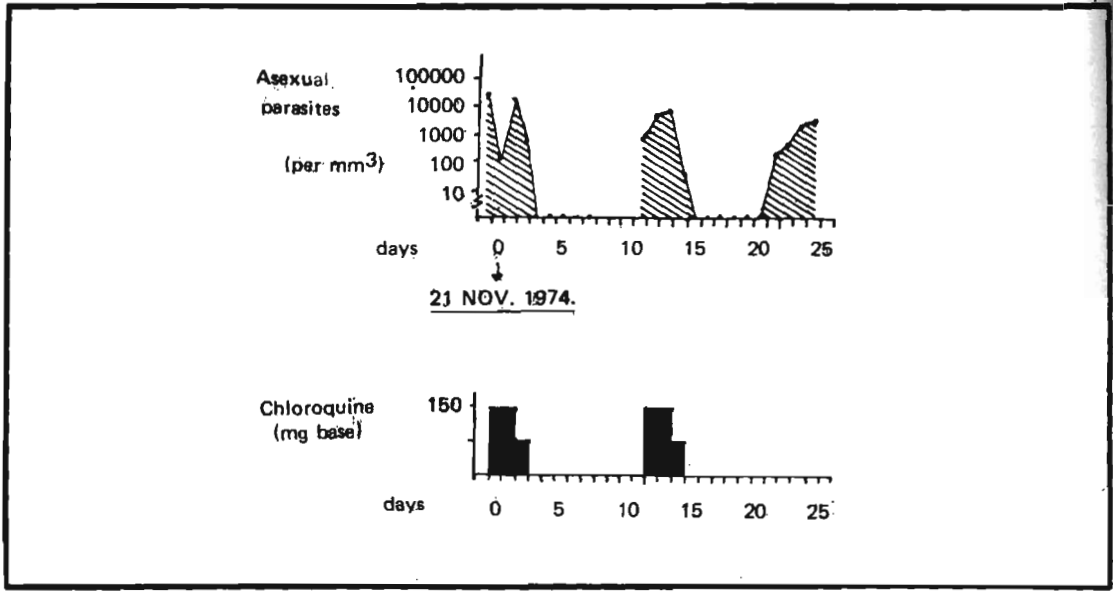

Figure II Effect of Chloroquine on a *P. Falciparum* strain from Jayapura

She was hospitalized in the provincial hospital and a second treatment was started on 3 December 1974. Asexual parasites again disappeared on day 3 only to reappear on day 9 of this second test.

A heparinized blood sample was taken on 15 December and flown to Jakarta where, on 17 December, it was glycerolized and frozen at -60°C in the NAMRU* laboratory.

Patients found positive on day 21 of the tests:

Of the other 27 patients who could be followed up until day 21 (or 22), 6 were found again positive, one with a very low parasitaemia, all the other 5 with *P. falciparum* asexual forms ranging from 140 per mm^3 to 5500 per mm^3. In these cases parasitaemia therefore reappeared between day 14 and 21.

It is to be noted that patient 7 released from hospital on day 14, was again found positive with an already high parasitaemia on day 21 (5500 per mm^3).

DISCUSSION AND CONCLUSION

In Hamadi Gunung, the predominant species is *P. vivax*, one would therefore have expected a few reintection with *P. vivax* but all patients found again positive on day 21 show *P. falciparum* infections.

Of the 3 parts of Hamadi, Hamadi Gunung is the area with the lowest parasite rate and therefore lowest transmission but it is the area where 5 cases were found again positive.

In Hamadi Gunung, there were 3 cases in which the asexual parasitaemia disappeared only on day 4. Two of these 3 cases were again positive on day 21. It is to be noted also that out of the 9 cases in which asexual parasites disappeared only on day 3 and which were followed up untill day 21, 5 were again positive on day 21.

It is understood that reinfection cannot be excluded but for the above reasons it is considered that probably most of the cases found again positive on day 21 were delayed recrudescences. Moreover, in patient 7, the possibility of reinfection is highly improbable considering the short period, following his release from hospital, during which asexual parasitaemia reappeared. This period is hardly compatible with the prepatent period of *P. falciparum*. At any rate the diagnosis of early recrudescence (day 9) is evident for the twice treated and hospitalized patient (table 5 and fig. II).

Table 5 Results of test for P. falciparum strain sensitivity to a standard dose for chloroquine in patient Wonda

Name : Yvonne Wonda (Slide No.: B210)

Age : 5 Sex : F Weight (kg) : 13

Condition : serious (on day 0), fever, sweating, headache, spleen 2

Locality : Hamadi Gunung

Origin : indigenous. Daughter of village chief

Date of first administration of chloroquine (day 0) : 21 November 1974

Particulars of chloroquine tables : chloroquine phosphate

Brand and Origin : Avloclor (imported)

Dose of base per tablets : 150 mg base.

* Naval Medical Research Unit (USA).

Date	Day	P. falciparum				Drug, dose mg base	Urine test Mayer Tanret	Remarks
		Trophozoites		Gametocytes				
		count*	per mm³	count*	per mm³			
20 Nov.	-1	936	32660	0				symptoms +
21 Nov.	0	3	105	0		150 mg	not done	
22 Nov.	1	563	19505	0		150 mg	+	
23 Nov.	2	25	875	0		75 mg		
24 Nov.	3	0	0	0				
25 Nov.	4	0	0	0				
26 Nov.	5	0	0	0				
27 Nov.	6	0	0	one only seen				
28 Nov.	7	0	0	0				
29 Nov.	8							
30 Nov.	9							
1 Dec.	10							
2 Dec.	11	28	980	0				
3 Dec.	12(0)	204	7140	0		150 mg	0	
4 Dec.	13(1)	264	9240	0		150 mg	+	
5 Dec.	14(2)	2	70	0		75 mg		
6 Dec.	15(3)	0	0					
7 Dec.	16(4)	0	0	0				
8 Dec.	17(5)	0	0	0				
9 Dec.	18(6)	0	0	0				
10 Dec.	19(7)	0	0	0				
11 Dec.	20(8)	0	0	0				
12 Dec.	21(9)	9	315	0				
13 Dec.	22(10)	20	700	0				
14 Dec.	23(11)	123	4305	0				
15 Dec.	24(12)	140	4900	0				IV blood collected

* per 200 leucocytes.

Moreover, two imported chloroquine-resistant falciparum infections (RI) were detected recently in Japan, in Japanese who had worked respectively in the Manokwari area and in the Kimi Bay area near Nabire. (I. Ebisawa, personal communication).

Another imported resistant falciparum infection was detected recently in England by Manson-Bahr in an English biologist who had visited various parts of Irian Jaya. The strain was sent to the Maryland school of Medicine and subinoculated into volunteers for drug characterization. This strain is resistant at the RII level to chloroquine 1.5 g over 3 days, RIII to pyrimethamine 150 mg over 3 days, RI to quinine, 2 g daily during 14 days and breaks through prophylaxis using proguanil (paludrine) 100 mg each day (D.F. Clyde, personal communication).

These results suggest a widely scattered distribution of chloroquine-resistant falciparum infections in Irian Jaya.

SUMMARY

The WHO Standard Filed Test for assessing the response of *P. falciparum* to a standard dosage of chloroquine base (25 mk/kg over 3 days) was carried out in 35 partially immune subjects from the outskirt of Jayapura, the capital of Irian Jaya.

There was no evidence of resistance at the RII or RIII level but in one patient, twice tested, early recrudescences (RI) were observed, one occuring on day 9 of the second test carried out in the provincial hospital. Among twenty seven other patients followed up until day 21, six were found again with asexual parasites. Other results suggest a widely scattered distribution of chloroquine resistance in Irian Jaya.

ACKNOWLEDGEMENTS

The authors acknowledge the assistance of Mr. W. Rooney, WHO Laboratory Specialist

and Mr. Karnadijaya, senior technician, Reference Malaria Laboratory, They are very grateful to Dr. Surjadi Gunawan, Provincial Chief Medical Officer, to Dr. A.M. Hutapea, Provincial CDC Chief and to Dr. Hilas J. Songan, Director, Provincial General Hospital, Jayapura, for their kind assistance and cooperation. Thanks are also due to the hospital doctors and malaria microscopists who participated in the study.

REFERENCES

Meuwissen, J.H.E.T. (1961) Resistance of *Plasmodium falciparum* to pyrimethamine and proguanil in Netherland New Guinea. Am. J. Trop. Med. Hyg., 10, 135

Peters, W. (1974) Drugs for the treatment and prophylaxis of malaria. Papua New Guinea Med. J., 1791

Verdrager, J. & Arwati (1974) Resistant *Plasmodium falciparum* infection from Samarinda, Kalimantan, Bull. Hlth. Studies in Indonesia, 2, 43

Verdrage, J. & Arwati (1975) Effect of a single dose of minocycline on a chloroquine resistant falciparum infection from Balikpapan, Kalimantan, Bull. Hlth. studies in Indonesia, vol. III, 2, 41

WHO., (1973) Chemotherapy of malaria and resistant to antimalarials, Report of a WHO Scientific group, Wld. Hlth. Org. techn. Rep. Ser., No. 529